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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/995,100	11/27/2001	Kunio Hori	15111	3176

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EXAMINER	
LU, FRANK WEI MIN	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 08/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/995,100	HORI ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *7-10,14-20,23,25 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,11-13,21,22 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office communication filed on June 2, 2005 has been entered. The claims pending in this application are claims 1-26 wherein claims 7-10, 14-20, 23, 25, and 26 have been withdrawn due to restriction requirement. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the response filed on June 2, 2005.

Priority

2. Note that applicant has filed certified copies of Japan application Nos. 2000-87501, and 2000-087504 on June 2, 2005. However, applicant has not submitted certified copies of Japan application No. 2000-087500 and this is no such document in this instant application.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Enablement

Claims 1-6, 21, and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting a polymorphism in a test sample containing a polymorphism site by optically measuring and analyzing a change of a fluorescent dye at a plurality of time points when the test sample is a DNA, does not reasonably provide enablement

for detecting a polymorphism in a test sample containing a polymorphism site by optically measuring and analyzing a change of any kind of marker substance at a plurality of time points when the test sample is any kind of sample. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court considered the issue of enablement in molecular biology. The Court summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims. The Court also stated that although the level of skill in molecular biology is high, results of experiments in molecular biology are unpredictable.

To begin, there is no direction or guidance in the specification to show that a polymorphism in a test sample containing a polymorphism site can be detected by optically measuring and analyzing a change of any kind of marker substance at a plurality of time points when the test sample is any kind of sample. While the relative skill in the art is very high (the Ph.D. degree with laboratory experience), there is no predictability that a polymorphism in a test sample containing a polymorphism site can be detected by optically measuring and analyzing a change of any kind of marker substance at a plurality of time points when the test sample is any kind of sample.

Claims 1-3 and 21 are directed to a method of detecting a polymorphism site in a test sample containing a polymorphism site by optically measuring and analyzing a change of any kind of marker substance at a plurality of time points wherein the test sample can be any kind of sample. Claims 4-6 and 22 are directed to a method of detecting a polymorphism site in a test sample containing a polymorphism site by optically measuring and analyzing a change of any kind of marker substance at a plurality of time points wherein the test sample is a DNA fragment. The specification does not provide a guidance to show that detecting a polymorphism in a test sample containing a polymorphism site by optically measuring and analyzing a change of any kind of marker substance at a plurality of time points when the test sample is any kind of sample such as a protein sample. First, according to the specification, "polymorphism" refers either to a allele group containing a plurality of types of alleles occupying a single genetic locus or to individual alleles belonging to the allele group (see page 8) while according to Life Science Dictionary, polymorphism is defined as "difference in DNA sequence among individuals" (see attachment for polymorphism). However, claim 1 does not limit a test sample to a DNA sample. Second, according to the specification, "marker substance" is defined as "marker emitting a signal with much the same intensity any measuring time-points. For example, luminescent substances, fluorescent substances, magnetic substances, and radioactive materials are included" (see page 9, last paragraph bridging to page 10, first paragraph). However, the specification and available art do not show that all marker substances such as magnetic substances or radioactive materials can be optically measured and analyzed a change at a plurality of time points. Therefore, in view of claims 1-6, 21 and 22, it is unclear how to detect a polymorphism in a test sample containing a polymorphism site by optically measuring and analyzing a change of any

kind of marker substance at a plurality of time points when the test sample is any kind of sample such as a protein sample.

With above unpredictable factor, the skilled artisan will have no way to predict the experimental results. Accordingly, it is concluded that undue experimentation is required to make the invention as it is claimed. The undue experimentation at least includes to test whether a polymorphism in a test sample containing a polymorphism site can be detected by optically measuring and analyzing a change of any kind of marker substance at a plurality of time points when the test sample is any kind of sample such as a protein sample.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-3, 21, and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 1 is rejected as vague and indefinite because it is unclear how reacting a test sample containing a polymorphism site with a plurality of types of probes labeled with marker substances can cause a positional change of the marker substance at a plurality of time points in the course of the reaction. Please clarify.

8. Claim 24 recites the limitation "said optical determining" in the claims. There is insufficient antecedent basis for this limitation in the claim because there is no phrase "optical determining" in claims 11-13. Please clarify.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 1, 3, 4, 6, 11, 21, 22, and 24 are rejected under 35 U.S.C. 102(e) as being anticipated by Iris *et al.,* (US Patent No. 6,403,309, filed on June 11, 2002).

Regarding claims 1 and 3, Iris *et al.,* teach reacting a test sample containing polymorphism (ie., a nucleic acid sample containing a polymorphism) plurality types of probes (ie., a plurality of peptide-labeled polymorphism-specific oligonucleotide probes comprising distinguishable fluorescent markers) corresponding a plurality of types of the polymorphism site be identified of said test sample, said probes binding to said plurality of types of the polymorphism site with a high affinity and being so as to optically distinguish from each other (see claim 1 in column 33, column 2, lines 34-47, and column 3, lines 1-13 and 47-63); and optically measuring and analyzing a change of the marker substance at plurality of time points (ie., i) and iii) of step d) of claim 1 in column 33) in the course the reaction (ie. the process of claim 1 taught by Iris *et al.,* in column 33), thereby detecting types of polymorphism sites of said test sample as recited in claim 1 (see claim 1 in column 33) wherein the polymorphism site is a single nucleotide polymorphism as recited in claim 3 (see column 2, lines 23-33 and column 27, lines 18-27).

Regarding claims 4 and 6, Iris *et al.,* teach hybridizing a test sample DNA fragment containing a sequence of a polymorphism site (ie., a nucleic acid sample containing a polymorphism) with plurality of types of DNA probes respectively having sequences complementary to a plurality sequences be identified and contained in test sample DNA fragment, and labeled with a marker substance (ie., a plurality of peptide-labeled polymorphism-specific oligonucleotide probes comprising distinguishable fluorescent markers), said plurality of types of probes being set so as to optically distinguish from each other (see claim 1 in column 33, column 2, lines 34-47, and column 3, lines 1-13 and 47-63); and
optically measuring and analyzing a change of the marker substance at a plurality of time points (ie., i) and iii) of step d) of claim 1 in column 33) in the course of the hybridization (ie. the process of claim 1 taught by Iris *et al.,* in column 33), thereby detecting the polymorphism site as recited in claim 4 (see claim 1 in column 33) wherein the polymorphism site is a single nucleotide polymorphism as recited in claim 6 (see column 2, lines 23-33 and column 27, lines 18-27).

Regarding claim 11, since Iris *et al.,* teach preparing a test sample containing a polynucleotide (ie., a nucleic acid sample containing a polymorphism), mixing a test sample with DNA probes PR_1 to PRn labeled with a detectable marker and capable of specifically binding to polymorphism sequences PS_1 to PSn (ie., a plurality of peptide-labeled polymorphism-specific oligonucleotide probes comprising distinguishable fluorescent markers), thereby binding the DNA probes PR_1 to PRn to the polynucleotide, detecting the DNA probes PR_1 to PRn in a micro space (ie., one of locus in a plurality of loci on the addressable antibody array) and analyzing detection results to determine which one of the DNA probes PR_1 to PRn binds to the

polynucleotide, thereby determining which one of the polymorphism sequences PR_1 to PSn corresponds to a nucleotide sequence of the polymorphism site as recited in steps (1) to (4) of claim 11 (see claim 1 in column 33, column 2, lines 34-47, column 3, lines 1-13 and 47-63, and column 6, lines 10-18).

Regarding claims 21, 22, and 24, Iris *et al.,* teach that said optical determining includes measuring fluctuation of the marker substance (ie., measuring signal differences on distinguishable fluorescent markers) (see step (d) of claim 1 in column 33).

Therefore, Iris *et al.,* teach all limitations recited in claims 1, 3, 4, 6, 11, 21, 22, and 24.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 2, 5, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iris *et al.*, as applied to claims 1, 3, 4, 6, 11, 21, 22, and 24 above, and further in view of Palo (US Patent No. 6,556,296 B1, priority date: September 29, 1997).

The teachings of Iris *et al.*, have been summarized previously, *supra*.

Iris *et al.*, do not disclose that said detecting is performed by a confocal microscope, and said analyzing is performed by a fluorescent correlation spectroscopy as recited in claims 2, 5, and 12. However, Iris *et al.*, teach that the detectable label is detected by confocal microscopy as recited in claims 2, 5, and 12 (see column 19, second paragraph).

Palo teaches to measure fluorescence intensity fluctuations by combination of a fluorescent correlation spectroscopy and a confocal microscope (see column 1, fourth paragraph and claims 1 and 19 in columns 9-11).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 2 or 5 or 12 wherein said detecting is performed by a confocal microscope and said analyzing is performed by a fluorescent correlation spectroscopy in view of the patents of Iris *et al.*, and Palo. One having ordinary skill in the art would have been motivated to do so because Iris *et al.*, teach that any method known in the art is used for visualization or detection of a signal from the detectable label (see column 19, second paragraph) while Palo suggests that combination of a fluorescent correlation spectroscopy and a microscope during the process of measuring fluorescence would create a technology for monitoring fluorescence from single fluorophore molecules (see column 1, fourth paragraph). One having ordinary skill in the art at the time the invention was made would have a reasonable expectation of success to perform the method recited in claim 2 or 5 or

12 by measuring fluorescence intensity fluctuations by combination of a fluorescent correlation spectroscopy and a confocal microscope.

13. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Iris *et al.,* as applied to claims 1, 3, 4, 6, 11, 21, 22, and 24 above, and further in view of Fujimiya *et al.,* (US Patent No. 5,190,632, published on March 2, 1993).

The teachings of Iris *et al.,* have been summarized previously, *supra.*

Iris *et al.,* do not disclose that said polynucleotide is a gene for a human histocompatible antigen. However, Iris *et al.,* teach to perform their method using a nucleic acid sample from different sources (see column 25, lines 58-67 and column 26, lines 1-12).

Fujimiya *et al.,* teach that human histocompatible antigens have polymorphisms (see column 1, third paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 13 wherein said polynucleotide is a gene for a human histocompatible antigen in view of the patents of Iris *et al.,* and Fujimiya *et al.*. One having ordinary skill in the art would have been motivated to do so because Iris *et al.,* suggest that a nucleic acid sample from different sources are used in their method (see column 25, lines 58-67 and column 26, lines 1-12) because the simple substitution of one kind of polynucleotide sample from another kind of polynucleotide sample (i.e, a polynucleotide from a gene for a human histocompatible antigen) during the process of performing the method recited in claim 13 would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Conclusion

14. No claim is allowed.

15. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)272-0735.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

August 7, 2006

FRANK LU
PRIMARY EXAMINER